Scientific Abstract

It is estimated that 240,000 new cases of prostate cancer will be diagnosed this year and 45,000 men will die from this disease. The majority of men diagnosed with prostate cancer will have inoperable advanced disease. The standard method of treatment is castration, surgically or chemically, but the cancer eventually becomes androgen resistant, resumes growth, and kills the patient. Clearly new strategies to combat this very common disease are needed. Molecular approaches to cancer therapy has allowed characterization of some of the genetic events that contribute to neoplasia. Advanced prostate cancer uniformly has overexpression of protooncogene c-myc leading to uncontrolled prostate cancer proliferation. A new strategy to treat advanced prostate cancer utilizes murine retroviral vectors that have the inclusion of tissue-specific or inducible promoters within retroviral vectors which should theoretically target expression to allow selective expression within specific tumor cells. The mouse mammary tumor virus (MMTV) long terminal repeat (LTR) is expressed at high levels only in certain tissues in vivo: breast, prostate, salivary gland. We have employed an XM6:MMTV- antisense c-myc vector to transduce DU145 human metastatic prostate cancer cells to suppress c-myc overexpression. Infection of cultured DU145 cells by supernatants from cloned producer cells expressing antisense c-myc RNA (titer $8X10^5$ virions/ml) resulted in a greater than 75% reduction in the tumor size when cells are injected subcutaneously into male nude mouse model (compared with control MMTV-based viral vectors). Moreover, a single direct injection of MMTV-antisense c-myc viral media into established DU145 tumors produced a 86% reduction in tumor size. Histological evaluation of MMTV-antisense c-myc transduced DU145 tumors revealed marked stromal response including inflammation, necrosis, and apoptosis.

Based upon these findings, we have proposed a clinical trial to determine if injection of antisense c-myc retroviral vectors will induce regression of advanced prostate cancer. The patient population will consist of men who have failed standard therapy and have extensive biopsy or cytology-proven prostate cancer. In this protocol, transrectal ultrasound-guided retroviral quadrant injections into cancerous prostates will be performed daily for 4 days by replacing the biopsied core of malignant cells with retroviral vector medium. Only patients who have previously failed standard therapy for their cancer and who are expected to survive for 6 to 18 months will be included in this study.